REMARKS

Claims 8, 10, 15-23 and 36-40 are pending after entry of the amendments set forth herein. Claims 9, 11-14 and 24-35 are canceled without prejudice. Claims 8, 10 and 15 are amended. Claims 36-40 are added. Support for the amending language "leukemia stem cells having self-renewal capacity" and "disease progression" may be found in the specification at paragraph 10. The selection for cells having the markers set forth in newly added Claims 36 and 37 may be found in originally filed claim 6. The language of Claim 37, relating to an LSC with an activated β-catenin pathway, which can be inhibited with axin may be found at paragraph 41. Support for the amending language of Claims 39 and 40 may be found in the specification at paragraphs [30], [34], [65] and [119]. No new matter is added.

Claims 15-23 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Office Action asserts that the language of Claim 15 is a departure from the specification and the claims as originally filed. Applicants respectfully disagree. The specification teaches at paragraph 61 that "the presence of LSC in a patient sample can be indicative of the stage of the leukemia. In addition, detection of LSC can be used to monitor response to therapy and to aid in prognosis. The presence of LSC can be determined by quantitating the cells having the phenotype of the progenitor cell relevant to the specific leukemia." The specification thus teaches that selection of LSC from a patient sample, using the method steps set forth in, for example, Claims 8 and 10, is useful in characterization of a leukemia sample.

The specification then teaches at paragraph 63 that "in addition to the presence of LSC, analysis of normal and leukemic hematopoietic samples allows determination of the stage of a leukemia. During progression of leukemic disease, which as used herein may refer to pre-leukemic and leukemic conditions, there is a significant expansion of $CD34^+$ cells in the blood, and a dramatic decline in these populations after successful drug treatment. Even more striking is the identification herein of shifting distributions of cells within this compartment, where the differential distribution of cells in the HSC, CMP, MEP and GMP populations is highly correlated with the stage of disease in myelogenous leukemias."

Thus, the specification teaches that as a part of a single method, one may select for leukemia stem cells, and further analyze for the distribution of cells with proghenitor compartments in order to provide for a more complete characterization.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

Claims 15-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner has questioned how one can characterize stem cells using the markers set forth in the present claims. Applicants submit that the answer lies in the present invention. It has been known for a long time that hematopoietic stem cells (HSC) are $CD90^+$ (and also $CD34^+CD38^+$), while progenitor cells are among other markers, $CD90^-$. As a result of this conventional wisdom, it was believed for many years that a leukemia stem cell would share the phenotype of the non-leukemic HSC.

It is the surprising and unexpected finding of the present application that the leukemic stem cell has the phenotype, not of the HSC, but of a progenitor cell. In leukemia, a progenitor cell that would normally lack activated self-renewal pathways, acquires this property, and , acquires this property, along with the ability to cause disease. Interestingly, it has been found that markers thought to be characteristic of certain leukemias, such as chromosomal translocations, can be found in non-tumorigenic HSC. It appears that until cells differentiate to the progenitor cell stage, there may be controls in place that prevent the cells from being tumorigenic.

In summary, while a normal hematopoietic stem cell is $CD90^+$, the progenitor cells that give rise to leukemia stem cells are $CD90^-$.

In view of the above remarks, withdrawal of the rejection is requested.

Rejections Under §102

Claims 8-10 have been rejected under 35 U.S.C. 102(a) as being anticipated by Jamieson et al (IDS). Applicants respectfully submit that the Jamieson et al. abstract was not published prior to the filing of the priority document for the present application. The cited abstract was presented at the 45th annual American Society of Hematology conference, which was held on December 6-9, 2003. US provisional application 60/527,411, to which the present application claims priority, was filed on December 5, 2003. Applicants respectfully submit that

the cited document is not prior art to the present application. Withdrawal of the rejection is requested.

Claims 8-10 have been rejected under 35 U.S.C. 102(b) as being anticipated by Petzer et al (IDS) or Duhrsen et al (IDS). The Office Action states that the cited references teach a method for selection of leukemia stem cells comprising using reagents that specifically recognize Thy-1 and IL-7Rα. Applicants respectfully submit that the presently claimed invention is not taught or suggested by the cited art.

With respect to Duhrsen *et al.*, the reference relates to experiments performed with mouse leukemia cell lines that are referenced as either PGM-1 or PGM-2. These cells lines differ from the leukemia stem cells of the present invention in that the cell lines are not found in naturally occurring leukemias, because they have been passaged in mice to achieve variants (see column 1, paragraph 3); because they are mouse cell lines, not human cells, and because the cell lines differ in phenotype from the leukemia stem cells described in the instant application. For example, the claimed LSC populations are lineage negative, while those described in the Duhrsen reference are stated to be positive for markers such as CD5 (see page 2630, paragraph 2).

In fact, the reference notes with respect to human leukemia stem cells that "primary human leukemias are poor in vitro test systems for the concept of differentiation therapy. Stem cells cannot be identified . . . " (page 2627, paragraph 2, underlining added).

In view of the above amendments and remarks, applicants respectfully submit that the present claims are not taught or suggested by the cited art. Withdrawal of the rejection is requested.

With respect to Petzer *et al.*, the reference relates to methods of analyzing cells having a "Philadelphia" chromosome translocation, typical of chronic myelogenous leukemia, where the cells had the phenotype of an otherwise normal hematopoietic stem cell. rather than assessing the tumorigenic properties of the cells, the authors assessed the ability of the cells to perform in a long term culture assay, which assay would read out as positive for any HSC that was present. Not surprisingly, the authors found that cells that were Thy-1^+ (indicative that the cells were HSC), read out in the assay.

As discussed above with respect to 35 U.S.C. 112, it is an interesting aspect of tumor biology that cells having the phenotype of a hematopoietic stem cells, and a chromosomal translocation associated with leukemia, are not tumorigenic cells, and do not themselves contribute to disease progression.

This point is made clear by the findings of Petzer et al., who found that:

> **In this report, we have shown that very primitive, genotypically normal hematopoietic cells, identified functionally as LTC-IC, are readily detectable in the PB of many CML patients in the chronic phase of their disease, even before the initiation of any treatment. Moreover, their numbers may exceed those typical of the PB of normal individuals, suggesting that normal as well as leukemic LTC-IC can be mobilized by the disease process. Perhaps the most unanticipated finding was that the numbers of these normal LTC-IC also frequently exceeded the number of Ph^+ LTC-IC present in the same CML PB samples (Table 2) as that in our previous studies of CML patients with high WBC counts in which predominantly Ph^+ LTC-IC had usually been observed.[11]**

Applicants respectfully submit that the cited art fails to provide for a leukemia stem cells, as presently described, in which the cells are both CD90 negative, and have the ability to self-renew and to maintain disease preogression.

In view of the above amendments and remarks, withdrawal of the rejection is requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-340.

Respectfully submitted,
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Date: Feb. 10, 2010

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